Environmental Health Perspectives
Vol. 38, pp. 143-146, 1981

Estrogen Receptors and Breast Cancer

by R. I. Nicholson,* K. Griffiths,* R. W. Blamey,† H. M. Bishop,† and J. L. Haybittle‡

Estrogen receptors have been assayed in a series of primary breast cancers from postmenopausal women; 59% of which were estrogen-receptor positive. These patients survived for a significantly longer period of time than those whose tumors were estrogen-receptor negative. The effect of estrogen-receptor status was only seen (and then markedly accentuated) in patients who had lymph-node invasion at the time of mastectomy. Such determinations also appear to be of value in preselecting those patients who, on recurrence, will benefit from tamoxifen therapy.

Introduction

One of the most striking features about breast cancer is that there appears to be at least two distinct practical categories of the disease. There are those tumors which are hormone-responsive and which will regress following the removal of, or interference with, their hormonal environment; objective breast tumor regressions often with extensive remission intervals are observed in approximately 30% of patients following the surgical removal of their ovaries, adrenal glands, or pituitary gland, or after the addition of pharmacological amounts of hormones or antiestrogens; there are other tumors whose growth appears to be independent of any substantial hormonal association and which derive little measurable benefit from these endocrine treatments. Although little is known about how these types of disease arise from the normal epithelium of the breast and indeed, what agents both endogenous and environmental, act to initiate and regulate their development, growth and interrelationships with one another, nevertheless it is apparent that they do represent extreme biological variants, and anecdotal evidence suggests that they are reflected in other fundamental and highly variable characteristics of the tumor, such as their degree of differentiation, their growth rates, and possibly even their invasiveness.

Currently, the most widely and successfully used method for the determination of the hormone responsiveness of breast tumors is the measurement of the intracellular concentration of a protein referred to as the estrogen receptor (*1*). This protein is present in the cytoplasm of hormone-responsive tumor cells and binds incoming estradiol with selective high affinity. The binding of the hormone to the receptor (ER) is then thought to facilitate the transfer to and retention of the receptor complex within the nucleus and thereby increase transcription of the DNA template, a process essential for cell maintenance and division. Clinical studies indicate that while the presence of ERs in secondary recurrent breast cancer is associated with a 50-60% objective breast tumor response rate to endocrine measures, in their absence only 5-10% of patients respond to these treatments (*2*). Such data have led to the routine use of ER measurements in breast cancer specimens in preselecting patients most likely to derive benefit from these endocrine therapies.

Furthermore, it has recently become evident that women whose primary tumors are ER-positive have a significantly longer disease-free interval, in the absence of any systemic therapy, than those who have ER-negative tumors, and that when ER status is combined with the lymph-node staging of the disease, both parameters act together to provide an accurate means by which early recurrence may be predicted (*3*, *4*). The present report extends

*Tenovus Institute for Cancer Research, Welsh National School of Medicine, Heath, Cardiff, U.K.
†Department of Surgery, University of Nottingham, U. K.
‡Department of Medical Physics, New Addenbrooke's Hospital, Cambridge, U. K.

these initial observations to examine the value of such ER measurements in relation to the survival of the patient. In addition, ER analysis on primary breast tumor specimens has been examined with respect to the response of the secondary disease to endocrine therapy.

Materials and Methods

Patients

Between 1973 and 1977, 250 women, aged between 27 and 75 years, with primary operable breast cancer, who consecutively presented to one surgeon (RWB), underwent a simple mastectomy and triple lymph-node biopsy (*5*). Of these women, 148 were postmenopausal and ER status was measured on 133 of these. All patients have been followed up for at least 2 years.

At mastectomy, lymph node biopsies were removed from the lower axilla, from the apex of the axilla and from the internal mammary tumor chain at the second intercostal space. Patients with no tumor histologically evident in any node were classified as Stage A; those with tumor only in nodes from the low axilla were classified as Stage B and patients with tumor in lymph nodes at the apex of the axilla or in the second intercostal space were designated Stage C. Patients were followed up at a postmastectomy clinic at 3-month intervals to 18 months and thereafter at 6-monthly intervals and have not been subjected to any form of adjuvant therapy.

Survival curves were derived from life-table analyses of the data at each follow-up time. Comparison between the curves were made with techniques described by Haybittle and Freeman (*6*)—an approach which evaluates differences between the whole curves rather than individual points on the curve.

For this study recurrence was defined as the development of symptomatic distant metastases confirmed by x-ray, abnormal liver function tests, or brain action. Once symptomatic recurrence was diagnosed, the first line of endocrine treatment in premenopausal women was oophorectomy and in postmenopausal patients tamoxifen therapy (10 mg b.d.). In addition, radiotherapy was given to particular sites (e.g. vertebral metastases) when indicated. Patients who failed to show objective response to endocrine treatment when assessed six months after initiation of therapy were treated with combination chemotherapy, as were patients showing obvious tumor progression two months after the initiation of endocrine therapy. Patients who showed objective response after six months endocrine therapy received secondary endocrine therapy in the form of adrenalectomy, once the response had ended.

Estrogen Receptors

At operation a representative portion of the primary tumor was frozen in liquid nitrogen and stored at –70°C before being transported in Dry Ice to the Tenovus Institute for subsequent ER assay. Details of the assay have been previously reported (*3*). Tumors were considered positive only when they contained more than 5 fmole specific estradiol binding/mg cytosol protein.

Results

ER Status and Survival

Of the 133 postmenopausal women, 79 (59%) were ER positive and 54 (41%) ER negative. To date 39 have died. Figure 1 shows the survival curve for patients with ER-positive tumors against that for patients with ER-negative tumors. Patients with ER-positive tumors survive longer than those with ER-negative tumors ($p < 0.025$). Furthermore, it was observed that there was no additional advantage for those patients whose primary tumor contained receptor levels in excess of

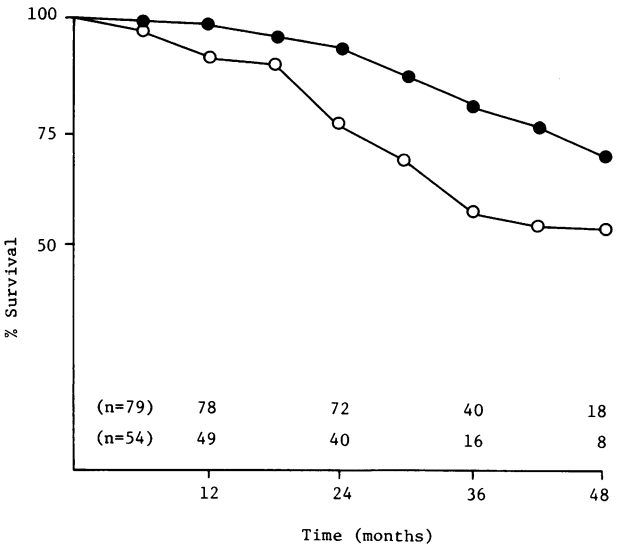

FIGURE 1. ER status and survival. Percentage survival of 133 postmenopausal women undergoing simple mastectomy: (●) ER +; (O) ER -. Numbers above abscissa indicate numbers of women remaining in the study at each follow-up point.

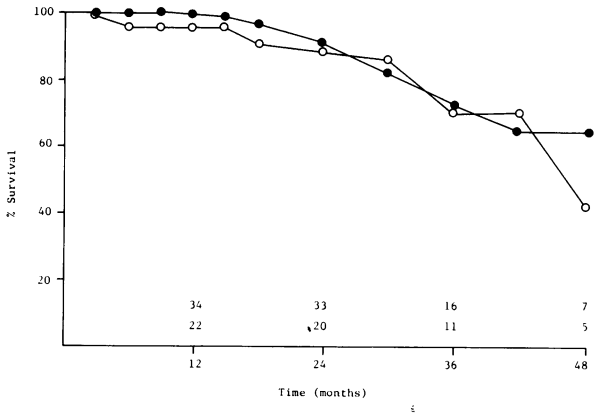

FIGURE 2. Survival and concentration of ER. Percentage survival of 57 postmenopausal women undergoing simple mastectomy in relation to concentration of ER: (o) ER+, 5-20 fmole/mg protein; (•) ER+, 21-100 fmole/mg protein.

100 fmole/mg protein (Fig. 2). When postmenopausal patients were analyzed according to tumor stage (Fig. 3), the effect of ER status was only seen (and was then markedly accentuated) in patients who had lymph-node invasion at the time of mastectomy. These correlations were not observed in premenopausal women where ER assays may be distorted by endogenous estrogens.

ER Status and Response to Endocrine Treatment

Table 1 shows the tumor response rates to endocrine therapy in patients with recurrent breast cancer in which the ER status of the primary disease was known. Of the 57 patients examined, 20 were premenopausal and underwent oophorectomy and 37 were postmenopausal and received tamoxifen (Nolvadex, ICI 46474). The overall response rates to oophorectomy and tamoxifen were 30 and 32%, respectively. Eleven out of 20 premenopausal women were ER-positive and of those 4 (36%) responded to oophorectomy. Of the nine premenopausal patients who were ER-negative, 2 (22%) responded to oophorectomy. In the postmenopausal group 19 out of 37 (51%) were ER-positive and of these 9 (47%) responded to tamoxifen. Out of the 18 postmenopausal patients who were ER-negative, 3 (17%) responded to tamoxifen.

Discussion

The present data clearly demonstrate that postmenopausal women with ER-positive primary breast tumors survive significantly longer than those with ER-negative tumors. These data are consistent with our previous findings in which the length of the disease-free interval was found to correlate with tumor ER status (*3*). The fact that these relationships were established on the absence of adjuvant therapy suggests that the ER status of the primary tumor is a measure of the natural biology of the tumor. This concept is reinforced by the finding that ER status is related to tumor histological grade, well differentiated tumors rarely lacking ER proteins (*5*). Interestingly, the absence of a relationship between tumor stage (by lymph node status) and ER status makes these two prognostic factors synergistic in the assessment of prognosis. This synergism has been demonstrated by our analysis of the effect in disease-free interval (*3*) and survival (*7*) (Fig. 3).

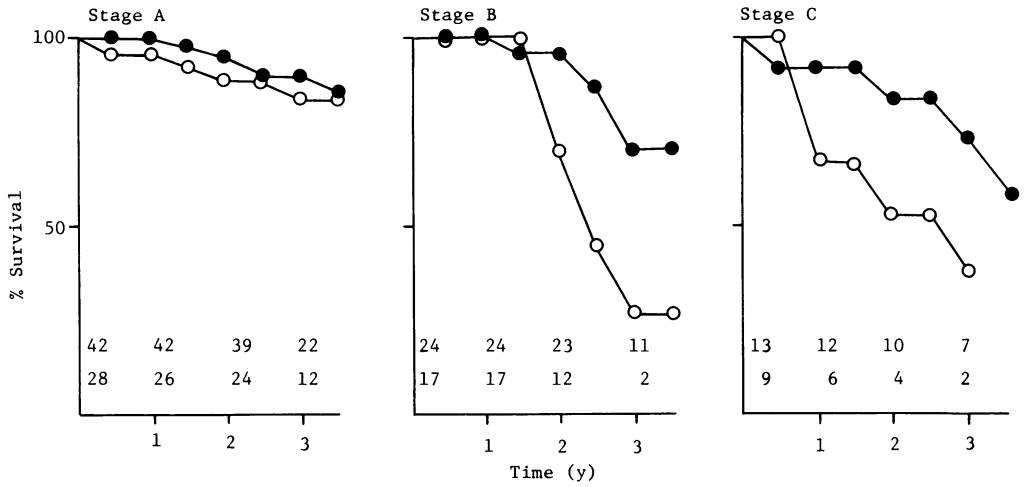

FIGURE 3. ER status, tumor staging, and survival. Percentage survival of 133 postmenopausal women undergoing simple mastectomy in relation to ER status and lymph node staging: (•) ER+; (O) ER-.

Table 1. Response to endocrine therapy.[a]

	ER +	ER −
Premenopausal (oophorectomy)	4/11 (36%)	2/9 (23%)
Postmenopausal (tamoxifen)	9/19 (47%)	3/18 (17%)

[a]Receptor analysis was carried out on primary breast tumor specimens.

In addition to the prognostic value of ER measurements in primary breast tumor tissue, such analyses also appear to be of some value in predicting the response of metastatic disease to tamoxifen therapy in postmenopausal women. In patients with ER-positive tumors the response rate of 47% is "similar" to that observed when ER measurements are carried out on metastatic deposits (*8*). This effect was not however, observed in premenopausal women undergoing oophorectomy where only 36% (4/11) of patients with ER positive tumors underwent an objective breast tumor remission, a value only slightly higher than the overall response rate (30%) for this group. Conversely, the response rates of 23% (2/9) and 17% (3/18) to oophorectomy and tamoxifen therapy respectively in patients with ER-negative primary tumors are higher than would have been predicted on the basis of ER measurements carried out on secondary breast tumor tissue (*2*). The numbers are at present, however, small. Also the study is in its early stages and is dealing at present with tumors of short disease-free interval. A further period of observation is now required to truly assess the value to the clinician of ER measurements in primary breast cancer tissue in relation to the subsequent response of the secondary disease to endocrine therapy. This is of obvious importance in that primary tumor tissue is always accessible to the surgeon and is of better quality for the biochemist than is secondary tissue.

The authors wish to acknowledge the generous financial support of the Tenovus Organization.

REFERENCES

1. Jensen, E. V., Mohla, S., Gorell, T. A., and DeSombre, L. R. Vitam. Horm. 32: 89 (1974).
2. McGuire, W. L., Carbone, P. P., and Voller, E. P., Eds. Estrogen Receptors in Human Breast Cancer. Raven Press, New York, 1975.
3. Maynard, P. V., Blamey, R. W., Elston, C. W., Haybittle, J. L. and Griffiths, K. Estrogen receptor assay in primary breast cancer and early recurrence of the disease. Cancer Res. 38: 4292 (1978).
4. Cooke, T., George, D., Shields, R., Maynard, P. V., and Griffiths, K. Oestrogen receptors and prognosis in early breast cancer. Lancet i: 995 (1979).
5. Maynard, P. V., Davies, C. J., Blamey, R. W., Elston, C. W., Johnson, J., and Griffiths, K. Relationship between oestrogen-receptor content and histological grade in human primary breast tumors. Brit. J. Cancer, 38: 745 (1978).
6. Haybittle, J. L., and Freedman, L. S. Some comments on the logrank test statistic in clinical trial applications. Statistician, 28: 199 (1979).
7. Bishop, H. M., Blamey, R. W., Elston, C. W., Haybittle, J. L., Nicholson, R. I., and Griffiths, K. Relationship of estrogen-receptor status to survival in breast cancer. Lancet i: 283 (1979).
8. Mouridsen, H., Palshof, T., Patterson, J., and Battersby, L. S. Tamoxifen in advanced breast cancer. Cancer Treatment Rev. 5: 131 (1978).